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R. B. Robins, M.D.

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R. B. ROBINS, M.D., was born October 27, 1899 in Ozan, Arkansas. He received his B.S. degree from Hendrix College in 1921; M.S. degree from the University of Chicago in 1923 and his M.D. from the University of Chicago in 1925. He has done postgraduate work at the Schools of Medicine at Harvard University, University of Michigan and the University of Indiana. He is a Fellow of American College of Surgeons, Fellow of International College of Surgeons and Associate Fellow, American Therapeutic Society. Dr. Robins was President of the Arkansas Medical Society in 1942, Vice-President of the American Medical Association in 1950-1951, and President-elect American Academy of General Practice in 1951.

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EDITORIAL

Statistics in Medicine

FREDERIC R. STEARNS, M.D., *Editor*

Statistical evaluations are frequently found in clinical papers. Unfortunately, in many of these papers, the basic rules of statistics are not obeyed and, therefore, the results are not statistically significant. There are, of course, other medical statistics like those elaborated by the United States Bureau of Census, The Public Health Organizations and a number of insurance companies, the results of which are very revealing, although in most cases these statistics do not refer to the main questions in which the practitioner is interested, namely to diagnosis and treatment.

The study of man and his reactions to his internal and external invironment, as related to health and disease, is a study of variation. Therefore, it is the most essential step in beginning such a study to state clearly the problem because only in determining the problem, the proper kind of data can be collected and the proper method can be found in which this collection should be performed. After collection of the data, they should be tabulated in order to establish the variation of the data under examination when they are organized in different ways. In thus organizing or classifying, one is able to distinguish between two types of data: first, measurement data which can be identified numerically, such as weight and height, blood pressure and temperature; tabulation of these data shows a frequency with which such data occur - frequency distribution; second, attribute data which comprise those data which cannot be marked numerically such as diagnosis and stage of disease.

We shall briefly outline, without going into details, the foundations on which medical statistics are necessarily based. As it already was shortly expressed in a previous paper, the main premises for statistical evaluations are: first, that the law of great numbers is duly considered, which means that the population of tested individuals is as large as possible; a second premise is the selection of a homogeneous group in which the relevant characteristics are prevalent, while the unimportant ones may be omitted. Homogeneity should not only comprise the disease or syndrome, but also the duration of the illness and other features which are indispensable in securing homogeneity. Symmetry of the population under consideration is a third premise which generally refers to the distribution of responses to given stimuli. It also should be borne in mind that observation relative to pathological reactions have statistical significance only when they are weighed in relation to the quantity and pecularity of the whole population to which the pathological data refer.

Medical statistical results are generally presented in rates or in ratios; these results are essentially the outcome of statistical analysis which is a comparison of one set of data with another. Rates and ratios are applicable for attribute data and, by means of certain characteristics of frequency distribution such as averages and measures of variation, also for measurement data. A rate is an expression of

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the number of times a specific kind of event occurs in a given population exposed to the possibility of its occurrence. A ratio expresses the relation of occurrence of a given kind of event to the occurrence of other events or of one kind of data to another. In order to give a few representative examples of rates and ratios, we give the following:

$$\text{Incidence rate} = \frac{\text{number of events in the population at risk during the specified time}}{\text{mean population at risk of event during specified time}}$$

$$\text{Case or morbidity rate} = \frac{\text{number of cases of a particular disease developing during a calendar period}}{\text{average population present during the same calendar period}} \times 1000$$

$$\text{Case fatality ratio} = \frac{\text{number of deaths from a particular cause}}{\text{number of cases of the same cause}} \times 100$$

$$\text{Prevalence ratio} = \frac{\text{number of cases of a particular disease at a particular time}}{\text{population at the same time}} \times 100$$

The final relationship of prevalence and incidence is $P = I \times D$; D is the average duration of the disease in an individual case stated in the same time units as I. This formula shows that shortness of D (acute infectious diseases) approximates prevalence and incidence, while length of D renders prevalence much greater than incidence (tuberculosis, syphilis, cancer).

There are two methods which are applied in scientific statistical evaluations and which are also important in clinical statistics, although they are not frequently found. The first is a so called "Index of Abmodality", which states that a found deviation from the norm is of significance only if related to the customary dispersion of data. For example, a deviation of 10 mm. from the average diastolic blood pressure is of no statistical significance unless compared with a diastolic blood pressure reading in the whole population of the same sex and the same age. When the deviation of the found data is brought into relation to the standard deviation of the data, the resulting measure is the Index of Abmodality. The second method to be mentioned is the so-called "Chi Square Test", which checks the valuation of actual data in relation to their theoretical distribution.

As stated above, the calculation of probability is the tool in predicting future developments. In uncomplicated conditions there are two standard principles underpining the theory of mathematical probability: (1) simultaneous occurrence of independent results. For instance, a married couple plans to have a family of four children. The probability that all four children are girls would be a little less than the fourth power of ½ as the ratio

of boys to girls at birth is about 1.06, (2) mutually exclusive results. In this case the probability that the choice will be one or the other is the sum of the probabilities. For instance, the statistical mortality rate of a certain surgical procedure has been found as being 10%; the statistical experiences of a lasting paralysis after the same operation is 25%. The probability, therefore, in a group of patients undergoing the same operations with succumbing to the operations or of remaining paralyzed is 1/10 plus ¼.

In short, mathematical probability states that if a group has n members and if m of them have a certain characteristic, the mathematical probability that an unspecified member of this class will have the characteristic in question is $\frac{m}{n}$.

These are very simple procedures of probability calculations. The probability of an event is seen to be a fraction which varies between 0 (impossibility) and 1 (certainty). Because of this linear function, probability calculations are frequently presented in curves which are called frequency curves. The frequency curve which characterizes probability is a so-called cumulative frequency curve.

It is not possible to go into the problem of probability calculations more throughly as it was only the purpose of this editorial to touch upon the methods which are indispensible for obtaining significant statistical results.

All statistical evaluations which do not follow the above mentioned principles and methods are generally not reliable and often misleading.

ORIGINAL ARTICLES

Gastric Analysis

Diagnostic Value of Intubation and Tubeless Techniques

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Introduction

Gastric analysis as a test in the study of the stomach function and disease was first introduced by von Leube in 1876. Kussmaul, Ewald, Boas, Einhorn and Rehfuss stand out as other pioneer workers in this field (1). Hollander and Penner in 1939 (2) reviewed the history and development of gastric analysis. Roth and Bockus (3) have discussed its indications and techniques.

This paper will concern itself with a brief discussion of the most common extant gastric analysis procedures as well as the indications and techniques of intubation and tubeless gastric analysis employed by the author.

It is obvious that gastric analysis is performed to study the gastric contents during a specific period of time under specific circumstances. The knowledge so obtained is cor-

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related with the subjective and objective findings to aid in the final evaluation of the patient's condition. In order to interpret the results of such analysis the normal physiological mechanism and contents of gastric secretion as well as the effect of local and general disturbances must be understood.

Pure stomach contents consist mainly of the products from the gastric glands and surface epithelium. The *parietal cells* secrete hydrocchloric acid and most of the fluid of the gastric juice. The *chief cells* secrete pepsinogen both into the stomach cavity and into the blood stream directly. The pepsinogen in the gastric juice becomes pepsin and that entering the blood is excreted into the urine as uropepsin. The *mucous cells* secrete a soluble mucoprotein which combined with the mucus from the surface epithelial cells forms gastric mucin.

The contents of the stomach obtained through intubation for gastric analysis are observed for odor, color, consistency, presence of regurgitated bile and swallowed saliva as well as extraneous material as blood, food particles, etc. The gastric contents will depend upon stimulating or inhibiting factors as well as abnormal conditions in or outside the stomach.

The most important determination in an average gastric analysis is the estimation of the gastric acidity. The secretion of gastric hydrochloric acid by the parietal cells is constant in composition and is independent of the nature or strength of the stimulus and rate of formation. It is the volume, not the concentration of parietal secretion, which varies and helps to determine the eventual concentration of the gastric acidity. Pure parietal secretion has an acidity of 159 clinical units (C.U.) (mEq./1). Yet the acid concentration of gastric contents usually is not above 60 C.U. (mEq./1). This is due to the changing proportion of parietal to non-parietal secretion as mucus, pepsin, etc.

The volume of gastric juice is usually parallel to the hydrochloric acid concentration. This is so because most of the water in gastric juice is secreted by the parietal cells. It thus follows that a high volume is usually accompanied by a high acid concentration. The volume, however, is not always a direct measurement or prediction of the acid concentration because duodenal juice, saliva and variations in mucus secretion affect the volume and thus indirectly the concentration of the hydrochloric acid.

There are many factors which directly influence the secretion of gastric acid. The hormone called gastrin and acetylcholine resulting from vagal stimulation are normally the two most potent forces in stimulating gastric secretion. It is thought that both gastrin and the vagus enhance each other's action or, in other words, vagus stimulation is less effective in the absence of gastrin, and gastrin is less effective in the absence of vagus activity. The vagal effect is usually central and is known as the cephalic phase. Gastrin production results from the action of secretagogues which are present in food as well as from distention of the stomach.

Inhibition of acid secretion can occur from the indirect effect of hydrochloric acid and fats upon the small intestine as well as from direct and indirect results of cephalic and sympathetic stimulation.

In expressing the gastric acidity, free acid, total acid and combined acid are stated as clinical units, mEq./1, mg. and/or pH. The exact meaning of these terms is obviously significant. Clinical units are used to define the degree of acidity that is present in 100 cc. of gastric contents as determined by neutralization of 100 cc. of gastric contents

by 0.1 normal sodium hydroxide. Thus, the amount of 0.1 normal sodium hydroxide required to neutralize 100 cc. of gastric juice determines the number of clinical units of acid present in 100 cc. of gastric juice. Since a clinical unit is equal to a milliequivalent of hydrochloric acid per liter of gastric contents, clinical unit and mEq./1 can be used interchangeably and it is probable that the term clinical unit will be replaced eventually by mEq./1. The reason for this is that mEq represents a definite equivalent of hydrogen ions and by knowing the amount of mEq./1, the total mEq. of hydrochloric acid output per unit of time can be calculated by measuring the volume of gastric secretion per unit of time. This can then be translated into milligrams, if so desired, by multiplying the number of milliequivalent of hydrochloric acid by the molecular weight of hydrochloric acid. The pH represents the hydrogen ion concentration or normality of the hydrochloric acid of the gastric juice. It can be determined accurately by any of the accepted pH meters or be calculated from the mEq./1 of hydrochloric acid. The reader is referred to an article by Hollander, "What Is pH?" (4), for further elucidation.

In clinical practice, free acid is usually determined by using dimethylaminoazobenzene (Topfer's reagent) as the indicator, which imparts an orange color at a pH of 3.5 and a yellow color at a pH of 4.0 (5). The total acidity is determined by using the indicator phenolphthalein which imparts a pink color at a pH of between 8.3 and 8.5. The difference between free and total acid is known as the combined acidity.

For practical purposes the physician may wish to know whether an individual secretes free acid or no free acid, and if he secretes free acid, whether it is secreted at a hyperacid, normal or hypoacid level. The normal range of free acid secretion is accepted as between 20 to 60 clinical units (mEq./1) (pH 1.8 to 1.3). Acidity above 60 C.U. is considered as hyperacidity and that between 1 to 20 C.U. (mEq./1) (pH 3.5 to 1.8) as hypoacidity. Achlorhydria is said to be present if no free acid is demonstrated by using Topfer's reagent as the indicator with the end point color change at a pH of 3.5. Complete anacidity is present if the pH is 8.3 or above. This is so because any pH between 3.5 and 8.3 signifies that some hydrogen ions are available and if some hydrogen ions are available, it means that some of the parietal cells secrete hydrochloric acid. The acidity between the pH of 3.5 and 8.3 represents the combined acid. A pH of 8.3 is used as the end point to signify that practically no hydrogen ions were available to be neutralized by gastric mucin, which has a pH of 8.3.

Intubation Technique

Gastric secretion obtained by intubation can be divided into the basal secretion and the secretion following a gastric secretory stimulant. In order to obtain both basal secretion and secretion after gastric stimulation, the gastric analysis is done as follows:

The Levine tube is inserted into the fasting stomach in the usual manner. The stomach contents are aspirated and this is called the fasting contents. Then the stomach is

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2. Hollander, F. and Penner, A.: History and Development of Gastric Analysis Procedure, Am. J. Dig. Dis. 5: 739, 1939; 5: 786, 1939; 6: 22, 1939.
3. Roth, J. L. A. and Bockus, H. L.: Why Do A Gastric Analysis?, Gastroenterology 18: 546, 1951.
4. Hollander, F.: What Is pH?, Gastroenterology 4: 497, 1945.
5. Shay, H., Komarov, S. A. and Berk, J. E.: Some Fallacies in the Clinical Measurement of Gastric Acidity with Special Reference to the Histamine Test, Gastroenteroscopy 15: 110, 1950.

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emptied completely every 15 minutes for one hour. The contents so obtained represent basal secretion. To learn the gastric acidity following stimulation, one of the various gastric stimulants is then administered and the gastric contents are collected every 15 minutes for one or two hours. The most common gastric stimulants are: 30 gm. of zwieback and 300 cc. of water, 50 cc. of 7 per cent alcohol, 500 mg. of caffeine sodium benzoate and 200 cc. of water, histamine as histamine diphosphate (0.1 mg. of the histamine base per 10 kg. of body weight or 2.75 mg. of histamine diphosphate per 10 kg. of body weight) or 15 units of regular crystallin insulin intravenously. The exact procedures are stated in laboratory manuals such as Ham's, "Syllabus of Laboratory Examination in Clinical Diagnosis." (6).

Tubeless Gastric Analysis

Indicator exchange compounds named *Diagnex,* which now make it possible to determine gastric acidity without subjecting the individual to intubation were prepared and first reported by Segal, Miller and Morton in 1950 (7). Further studies by Segal and his associates (8,9) of a specific indicator compound called *quinine exchange indicator compound* have demonstrated that this compound is a reliable agent to determine the ability of a stomach to secrete free hydrochloric acid without subjecting the individual to intubation. This compound is produced by replacing the hydrogen cations of a cation exchange resin, such as Amberlite XE-96 (Rohm & Haas Company), with quininium cations as the *special indicator cation.* When this compound is subjected to the action of dilute hydrochloric acid present in gastric juice, the quininium cations of the compound are displaced by the hydrogen ions of the hydrochloric acid with the formation of quinine hydrochloride. The quinine hydrochloride is absorbed in the small intestine and excreted in the urine. The presence or absence of quinine in the first two-hour urine excretion after the administration of this Diagnex* compound determines the presence or absence of free gastric hydrochloric acid.

The instructions for the patient are as follows:

Nothing to eat after midnight.

Save first urine, on arising, in brown bottle marked "Morning."

8:00 A.M.—Pour contents of Bottle I into 1 glass of water and drink this mixture.

Do not eat breakfast.

9:00 A.M.—Urinate, if possible, and discard the urine.

Put contents of tube marked "Granules" into a glass. Add ¼ glass water. (Granules do not dissolve) Stir vigorously with a spoon and drink immediately. (Do not chew the granules) Follow this by ¼ glass water. If any of the particles still remain in the glass, some of this water can be used for further stirring.

10:00 A.M.—(1 hour after taking granules) Urinate and save in correctly labeled brown bottle.

11:00 AM—(2 hours after taking granules) Urinate and save in correctly labeled brown bottle.

6. Ham, T. H.: A Syllabus of Laboratory Examination in Clinical Diagnosis, Harvard University Press, Pg. 310, 1950.
7. Segal, H. L., Miller, L. L. and Morton, J. J.: Determination of Gastric Acidity without Intubation by Use of Cation Exchange Indicator Compounds, Proc. Soc. Exp. Biol. and Med. 74: 218, 1950.
8. Segal, H. L., Miller, L. L., Morton, J. J. and Young, H. Y.: The Use of Cation Exchange Indicator Compound to Determine Gastric Acidity without Intubation, Gastroenterology 16: 380, 1950.
9. Segal, H. L.: Determination of Gastric Acidity without Intubation. The Clinical Evaluation of Quininium Exchange Indicator Compound, Med. Clin. N. A. 35: 593, 1951.

*The Diagnex Quininium Exchange Compound is now prepared by E. R. Squibb & Sons, 745 Fifth Avenue, New York 22, New York.

Empty the bladder completely each time. If you have to urinate before the time scheduled, save this urine and add it to that passed at the designated time. The quinine present in the urine samples is extracted by the use of ether and aqueous sulphuric acid (10). The aqueous sulphuric acid solution thus obtained is viewed in ultraviolet light and compared with standard concentrations of quinine sulphate. The presence of a trace or more of quinine in the urine signifies the presence of free gastric hydrochloric acid. The absence of quinine or the presence of a very faint trace signifies the absence of free gastric hydrochloric acid.

Indications

There are definite indications to determine the presence of achlorhydria and the degree of acidity when free acid is present.

The determination of achlorhydria is probably the most important one in the study of gastric secretion. Achlorhydria is of significance in the diagnosis of carcinoma of the stomach, in differentiating between a malignant and benign gastric ulcer, in ruling out duodenal ulcer in the pseudo-ulcer syndrome and in determining post-vagotomy insulin achlorhydria. It is of crucial importance in the diagnosis of primary pernicious anemia.

Achlorhydria occurs in about 5 per cent of the population in the third decade and increases with age to reach about 27 per cent or more people past 60 years of age (11). Although the presence of achlorhydria is compatible with good health and by itself does not constitute a definite diagnostic test, such information may be used in screening individuals for further studies.

Among the diseases and conditions that are associated frequently with achlorhydria (gastric carcinoma, atrophic gastritis, long standing ulcerative colitis, vitamin B-12 complex deficiency, iron deficiency anemia) (3) gastric carcinoma is of the utmost importance. The diagnosis of gastric carcinoma before symptoms appear can only be made by roentgenologic and gastroscopic examinations. The latter procedure is more or less impractical and thus a gastrointestinal roentgenologic study is the only practical means of making an early diagnosis of gastric carcinoma. Since achlorhydria is present in about 60-65 per cent of patients with gastric carcinoma, (11, 13) and since a larger percentage of individuals with achlorhydria in the gastric cancer age group develop gastric carcinoma than those of the same age group with free gastric hydrochloric acid (11, 14), it would be advantageous to find the achlorhydric individuals in the gastric cancer age group. Such individuals could then be submitted to frequent roentgenologic examinations for the early detection of gastric carcinoma. The tubeless gastric analysis technique now makes it feasible routinely to test for achlorhydria in all individuals in the gastric cancer age group. Moreover, this examination should become a routine procedure in annual physical examinations in everyone in the cancer age group because the occurrence of achlorhydria in individuals who previously had free acid may be the first objective evidence of gastric carcinoma.

In the case of pernicious anemia it is mandatory to make the exact diagnosis since it is unfair to sub-

10. Kelsey, F. E. and Geiling, E. M. R.: The Micro-Determination of Quinine in Blood and Tissues, J. Pharm. and Exp. Therap. 75: 183, 1942.
11. Comfort, M. W.: Gastric Acidity Before and After Development of Gastric Cancer, Ann. Int. Med. 34: 1331, 1951.
12. Levin, E., Kirsner, J. B. and Palmer, W. L.: A Simple Measure of Gastric Secretion. Comparison of One Hour Basal Secretion, Histamine Secretion and Twelve Hour Nocturnal Secretion, Gastroenterology 19: 88, 1951.
13. Barrett, M. K.: Avenues of Approach to the Gastric Cancer Problem, J. Nat. Cancer Inst. 7: 127, 1946.
14. Kaplan, H. S. and Rigler, L. G.: Pernicious Anemia and Carcinoma of the Stomach: Autopsies Studies Concerning Their Interrelationship, Am. J. Med. Sci. 209: 339, 1945.

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ject individuals to the expense entailed in the injections of vitamin B-12 indefinitely. The knowledge of the presence of free gastric hydrochloric acid would help to avoid such careless therapy.

In most patients in whom a gastric analysis is contemplated, a tubeless gastric analysis should be done first to rule out achlorhydria. If this test shows the presence of free hydrochloric acid, then the determination of the degree of acidity by the intubation technique will be indicated in the following circumstances:

1. A duodenal ulcer resistant to medical therapy: the basal secretion (12) and the degree of acidity after a gastric stimulant will help to direct a more energetic medical regime or aid in determining if and what type of surgery is indicated.

2. An ulcer syndrome with negative x-ray evidence: the basal secretion and the range of gastric acidity after stimulation with caffein sodium benzoate may demonstrate the presence or absence of ulcer potentiality (3).

3. Ulcer symptoms in post-vagotomy patients: in a post-vagotomy patient without a drainage operation the lack of hydrochloric acid after insulin will signify a complete vagotomy. In patients with vagotomy combined with gastroenterostomy, pyloroplasty or resection, positioning, of the Levine tube may be very important in evaluating the results.

Summary

The physiology of gastric secretion and indications for gastric analysis are discussed.

The intubation technique and a new technique for determination of achlorhydria without intubation are described.

The tubeless gastric analysis procedure consists of the oral administration of a quininium indicator exchange compound. Quinine is released from this compound in the presence of free gastric hydrochloric acid and then appears in the first two-hour urine excretion. The procedure for this test is described.

Most patients in whom gastric analysis is indicated should first be studied by tubeless gastric analysis. If free acid is present, a regular gastric analysis can be performed when indicated. The indications are outlined.

The importance of determining achlorhydria for both diagnostic and screening purposes is stressed.

Importance of Bone Marrow Studies in Clinical Medicine

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Examination of bone marrow in living patients is a relatively recent acquisition in the clinical diagnostic armamentarium. The first attempts at bone marrow biopsy[1] by trephining the femur (Pianese, 1909) or the tibia (Ghedini, 1910) proved to be too much in the nature of major operations, and therefore could not become an established clinical method. Moreover, these bones frequently do not contain a hematopoietically active marrow. Seyfarth[2] in 1923 first suggested trephining the sternum, a

much lesser procedure. However, it was not until Arinkin[3] introduced in 1929 the technic of sternal aspiration, that bone marrow studies became a routine clinical procedure. Since then aspiration of bone marrow has achieved considerable importance[4] as a diagnostic aid not only in the study of blood diseases, but also in certain other conditions, such as protozoal infections, metabolic bone diseases, etc. This article will outline the technics and diagnostic importance of bone marrow aspiration.

Technic of Bone Puncture for Obtaining Marrow

Choice of site. At present three sites are being routinely used for bone marrow aspirations: sternum, iliac crest, vertebral spines. When a patchy rather than a diffuse involvement of bone marrow is suspected, multiple punctures from different sites may prove of importance. In certain instances best results will be obtained if the site of puncture is carefully selected on the basis of clinical and roentgenological evidence of bone involvement (ribs, etc.). The more frequently used technics will be reviewed.

Sternal aspiration. The manubrium is preferable in infants and children, as it is safer and contains a cellular marrow until adult life. In adults, the area of sternum below the junction of the manubrium and the body is used. With the patient lying on his back, the skin, subcutaneous tissues and periosteum are infiltrated with 2% novocaine. A sternal needle furnished with a stylet is then driven through the outer table of the sternum by firm pressure (some prefer to give sharp, gentle taps from a small mallet). Many types of needle can be used; some have a guard to prevent perforation of the posterior plate of the sternum; these needles vary from 16 gauge to 10 gauge. A definite "give" is usually felt as the needle enters the marrow cavity. The stylet is removed and a 20 cc syringe attached, and gentle suction applied. A characteristic "suction pain" occurs if the needle is in the proper place.

Iliac aspiration. Until recently sternal aspiration was almost the only source of bone marrow studies in clinical medicine. In 1943 the author saw a patient with roetgenologic evidence of a single metastatic lesion in the iliac bone, and in an attempt to recover the neoplastic cells aspiration of the iliac lesion was performed. This proved to be easy to perform and yielded active bone marrow tissue. Following our reports[5] on several hundreds iliac bone marrow aspirations, this technic has been generally accepted in this country and abroad. The site for aspiration in the area of the iliac crest posterior to the anterior superior spine. The patient usually lies on his back, but in case of abdominal distention he is turned on his side. The puncture is performed with the needle held in the sagittal plane of the body. The needle is directed from the top of the crest downwards. As a rule a sternal puncture needle may be used also for the iliac aspiration.

Spinous process puncture. Katsuname in Japan was the first to use

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4. Monographs and reviews: K. Rohr, Das menschliche Knochenmark, G. thieme, Stuttgart, 2nd Edition, 1949. S. J. Leitner, Bone Marrow Biopsy, Grune and Stratton, New York, 1949. N. Rosenthal,: The value of the Bone Puncture for obtaining marrow as a diagnostic procedure, Bull. N.Y. Acad, of Med. 26:555, 1950.
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6. Loge, J. P. Spinous process puncture; simple clinical approach for obtaining bone marrow, Blood 3:198, 1948.

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this technic.[6] The most prominent spinous process (usually L3 or L4) is chosen. The puncture may be performed with the patient in the sitting position leaning forward. After infiltration with novocaine of the periosteum over the spinous process, a sternal puncture needle is pushed through the skin at an angle of 90 degree, and fixed midway between the upper and lower borders of the spinous process. The needle can be introduced also at one side of the spine, and then pushed medially, entering the bone anteriorly to the tip where the cortex is less thick.

Comparative value of sternal and iliac technics. Some disadvantages of the sternal technic have long been recognized. This procedure involving operation with a large needle in the cardiac area usually renders patients apprehensive, and not infrequently it is refused. Moreover, sternal aspiration is not altogether without real danger; although only a few fatalities have been recorded, the actual number of fatal outcomes or some serious complications is probably much larger.[5] On the basis of 300 cases where simultaneous studies of sternal and iliac bone marrow were performed, the following advantages of the iliac technic were indicated.[5] 1. Safety: no injury can be sustained by any underlying organ; 2: Ease: usually the iliac puncture is less painful and the patient less apprehensive than when subjected to a puncture in the heart area; 3. Repeated aspirations: iliac punctures can easily be performed at frequent intervals on both sides of the body, and therefore are very suitable for serial bone marrow studies.

Study of the aspirated material. After a small amount of marrow fluid is aspirated covering just the capillary part of the syringe (about 0.2 cc), the syringe is withdrawn, and direct smears, especially of visible bone marrow particles, are prepared, and total nucleated cell counts done. Immediately afterwards, with another syringe, 1 cc of the marrow is aspirated through the same needle, mixed with heparin and spun at 1.500 r.p.m. for five minutes. The marrow is thereby separated into four chief layers: fat, plasma, nucleated cells (myeloid and erythroid), and red cells; the proportions of these vary with hyperplasia or aplasia of different marrow cells. The concentration of certain elements which may be scanty in direct smears, make the procedure useful in some cases. This method has led to the finding in the buffy coat of the characteristic cells in lupus erythematosis in bone marrow[8] and peripheral blood.[9]

Also material for section may be obtained after fixation (40% formaldehyde or Zenker-formol solution) and embedding of the spun tissues. Bone marrow particles in clotted plasma can also be used for preparation of sections.

Importance of Bone Marrow

Bone marrow preparations thus obtained are studied for total cellularity, for cell distribution of hematopoietic elements, and for presence of foreign cells. In particular, cytologic examination of bone marrow includes determination of the myeloid-erythroid ratio, the degree of maturation within both the myeloid and erythroid series, the number of megakaryocytes and their ability to produce platelets, and any degree of invasive proliferation by any cell type (lymphatic, myeloid). In search for foreign elements, one may look for neoplastic cells, as well as for lipoid storing reticulum cells (Gaucher's cells, etc), and for certain protozoal bodies.

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Diagnostic Value of Bone Marrow

1. In blood diseases.

Certain hematologic disorders are associated with typical bone marrow pictures. Such is the case of pernicious anemia, where arrest of maturation of red cells produces the characteristic megaloblastic bone marrow; of leukemia, with infiltration of the bone marrow by the leukemic cells; in multiple myeloma with invasion by plasma-like myeloma cells. Frequently other clinical and X-ray findings and peripheral blood examination will point to the diagnosis. The characteristic bone marrow picture found in these instances will be then only of confirmatory diagnostic value. However, in a number of cases other diagnostic findings may be lacking or overlooked, and examination of bone marrow will be first to furnish the correct diagnosis. In the following paragraphs will be listed the main conditions where bone marrow studies proved to be of diagnostic importance (primary or confirmatory):

Leukemias: in all varieties of acute leukemia (myeloblastic, lymphoblastic or monoblastic), massive infiltration of bone marrow by the immature leukemic cells is the rule. In certain instances of leukemia, namely those designated as aleukemic variety, the peripheral blood picture may not show the presence of a characteristic increase of immature cells sufficient for diagnosis. The diagnosis, for example, can sometimes be suspected by the presence of lymphadenopathy or splenomegaly, and by such blood findings as anemia, thrombocytopenia, lymphocytosis. A similar picture, however, is so frequently found in other conditions that the diagnosis of aleukemic leukemia at times can only be made with absolute certainty by the finding in the bone marrow of a marked proliferation of immature cells in leukemic fashion. With the progress of the disease, these immature cells may appear later also in the blood.

Thus anemia with leukopenia and thrombocytopenia (pancytopenia) may be due to a number of different causes: hyperplenism, aplastic anemia, myelophthisic anemia, etc. If it is the result of leukemia in the "aleukemic" stage, bone marrow studies will permit a definite diagnosis to be made. I have seen a number of cases originally diagnosed as agranulocytosis due to sulfa-drugs or other chemicals, where bone marrow aspiration revealed the presence of leukemia. In one variety of leukemia, namely chronic myelocytic leukemia, the bone marrow may present a picture which is by itself not diagnostic of, but compatible with leukemia. It may be compatible also with other conditions (such as infections, malignancy etc.) attended by myeloid stimulation of bone marrow and sometimes also by a leukemoid reaction in the blood. However, acute exacerbations in the course of chronic myelogenous leukemia are associated with the appearance of a more immature myeloblastic marrow, and conversely, replacement of myeloblasts by more mature myelocytes portends usually a more chronic phase. Bone marrow study will therefore be of prognostic value in these cases of chronic leukemia.

Anemias. In the group of macrocytic anemias bone marrow studies will permit recognition of those cases that are due to arrest of red cell maturation at the megaloblastic stage. Thus in pernicious anemia in relapse and in macrocytic anemia of untreated sprue, megaloblastic anemia (such as in some cases of aplastic anemia, or hemolytic anemia, or leukemia) megaloblastic bone marrow is lacking.

In hemolytic anemias, whether congenital or acquired, acute or

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chronic, a normoblastic bone marrow is the rule. Occasionally, a transitory aplastic stage during a crisis, may be observed.

A normoblastic reaction of bone marrow is found also in iron deficiency anemias that are due most frequently to loss of blood.

In contrast, a depression of normoblasts as well as of other bone marrow elements, is seen in anemia (sometimes refractory to therapy) due to toxic conditions, such as nephritis, certain infections, or endocrine deficiencies.

A more severe hypoplasia or a total aplasia of all bone marrow elements is characteristic of aplastic anemia. In certain instances of aplastic anemia, however, the bone marrow is normal or even hyperplastic, there being an apparent difficulty in releasing the cells into the peripheral blood.

Thrombocytopenic purpuras. The bone marrow is of some importance in differentiating the various types of thrombocytopenic purpura, and in predicting the results of splenectomy to be expected in each type. Three varieties have been described associated with the following bone marrow findings: 1. Absence of megakaryocytes (the giant cells that produce platelets); 2. Normal or increased number of megakaryocytes; this is seen in the main forms of chronic idiopathic purpura. Arrest of maturation of megakaryocytes leads in spite of their number to inadequate platelet formation: 3. Normal picture of megakaryocytes may be found in some cases of thrombocytopenia accompanied by anemia and leukopenia, and splenomegaly (hypersplenism). It is considered that splenectomy is indicated only in thrombocytopenias of varieties (2) and (3), and that finding of aplasia of megakaryocytes predicts failure of splenectomy for cure of thrombocytopenia.

In a number of cases bone marrow aspiration may allow recognition of the secondary nature of thrombocytopenic purpura, and reveal the underlying disease, such as multiple myeloma or Gaucher's Disease. This is important, as splenectomy is generally contraindicated in secondary thrombocytopenia.

Multiple Myeloma. Although the diagnosis can be indicated by multiple bone lesions, hyperglobulinemia, Bence-Jones proteinuria, etc., some of these changes may be absent, and bone marrow findings will be of crucial diagnostic importance. Plasma like myeloma cell infiltration of bone marrow is typical.

In some cases of bleedings as presenting symptom that came to our observation, bone marrow examination revealed the unexpected diagnosis of multiple myeloma. It is important, however, to remember that moderate increase of plasma cells may be encountered also in conditions other than multiple myeloma, for example, cirrhosis of liver. It is important, therefore, to distinguish, whenever possible, the myeloma cells from the non malignant plasma cells.

2. *In Non Hematologic Conditions*

Inborn errors of lipoid metabolism. Bone marrow aspiration may be of crucial significance in the following three conditions of disturbances of various types of lipoid metabolism: 1. Gaucher's Disease, 2. Niemann-Pick's Disease, 3. Hand-Schiller-Christian's Disease. While the hemapoietic tissue of bone marrow may appear generally normal, there may be scattered in the smear preparation large reticulum cells showing various types of stored lipoid characteristic of the respective disease.

1. In Gaucher's Disease reticulum cells are characterized by the presence of needle-like crystals of kerasin, which gives a reticulated appearance to the cells.

2. Niemann-Pick's disease is characterized by foam-like cells contain-

ing a phosphatic substance.

3. Hand-Schiller-Christian's disease (xanthomatosis) shows reticulum cells containing cholesterol.

Protozoal infections. Other conditions where study of reticulum cells of the bone marrow is of diagnostic importance, are certain protozoal infections, with the parasites making their home in the reticuloendothelial system.[7] Bone marrow aspiration may reveal therefore phagocytosed organisms: in Kala-Azar, the Leishman-Donavan bodies; in Histoplasmosis, the Histoplasma Capsulatum organisms; in tertian malaria, plasmadium bodies.

Granulomatous diseases. In the diagnosis of granulomatous leions, the histological study of sections made from aspirated bone marrow material has in certain cases demonstrated lesions of brucellosis, Hodgkin's disease, sarcoidosis, miliary tuberculosis.

Disseminated Lupus Erythematosis. The diagnostic finding of "L.E." cells of Hargrave was first demonstrated in bone marrow aspirations.[8] The factor responsible for its formation resides in the gamma globulin fraction of the plasma, and it acts on the neutrophilic leukocytes causing the characteristic nuclear transformation. Therefore the "L.E." cells may be found in lupus patients not only in bone marrow, but also in normal blood incubated with the patient's plasma.[9]

Metastatic Malignancies. In a certain proportion of cases, malignant cells may be detected in the bone marrow, especially in carcinoma of the prostate, breast, thyroid, lung, kidney. These cells appear usually in clumps, and form a syncytium. Neoplastic cells are more frequently found in marrow aspirated from the iliac crest than in the sternal aspiration.[10] Occasionally in unrecognized malignancy bone marrow aspiration provided the first definite evidence of neoplastic disease. At other times, in proved primary malignancy it showed the presence of metastatic tumor cells despite the absence of X-ray evidence of osseous metastases, and thus was first to disclose the inoperability of cases that otherwise appeared to be operable. In our experience, in aspirating tumor tissue in a number of cases, no bone marrow could be obtained; instead a piece of solid tissue was recovered from the needle. When smears were made of this material, massive clumps of tumor tissue were found. A similar situation may be obtained in other conditions, such as lymphatic leukemia. We, therefore, made it a practice never to discard an apparently unsuccessful ("dry") tap without examining the contents of the needle.[11]

3. *Value of bone marrow aspiration in ruling out certain condition.*

While the enumerated instances show the value of marrow studies in establishing a definite diagnosis, in the majority of cases where the aspiration is performed its usefulness is in that it reveals normal findings, and permits one to rule out a suspected hematologic condition. This is of especial importance in certain infectious conditions (such as sepsis, infectious mononucleosis, etc.) that may simulate a leukemic blood reaction (leukmoid reaction, monocytosis, lymphocytosis), or in various leukopenic, agranulocytic and thrombocytopenic states. Bone marrow examination will serve to exexclude primary hematologic disorder.

Summary

In summarizing the presented survey of bone marrow studies in clinical medicine one may conclude that the value of this technically easy

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procedure is threefold:

1. In a restricted number of patients it was of *crucial* diagnostic importance. An unequivocal diagnosis was arrived at on the basis only of bone marrow aspiration studies.

2. In another, larger, category of instances it was merely of *confirmatory* diagnostic value. Bone marrow findings proved compatible with a previously entertained diagnosis.

3. In still another much larger group of patients, bone marrow aspiration is chiefly of value in *excluding* certain suspected conditions.

In conclusion, bone marrow aspiration is an easy procedure involving but little discomfort to the patient, and should be performed in any obscure clinical syndrome.

The Present Day Treatment of Frostbite

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Recent years have witnessed an intensive study on the effects of cold injuries with especial emphasis on the pathogenesis of the resulting lesions and the rationale of proposed treatment programs. Much of practical merit which is applicable to the management of frostbite whether occurring in civilian or military life has emerged from the many scientific investigations on the subject.

Any discussion of a therapeutic program for frostbite would of necessity be predicated on an understanding of its basic physiology and pathogenesis. There are two preponderant schools of thought for the explanation of the pathologic physiology. The one, led by Ungley, Blackwood and, more recently, Lewis, contends that tissue necrosis is caused by a direct-action of cold on the tissue cells causing a peripheral vasoneuropathy and producing a reduced blood supply, edema and extravasation of blood. The one group, including Green, Kreybert and Friedman presupposes the existance of tissue damage secondary to vascular changes, namely vasoconstriction, stasis and subsequent occlusive thrombosis of capillaries and arterioles.

The progression of changes in a limb exposed to cold are well known; Lange and his associates, in correlating the pathologic physiology, employed the fluorescein test and the capillary microscope along with histologic studies. The blanching which almost always occurs at the outset is due to arteriolar con-

striction and slowing of blood flow. The capillary permeability is decreased. Oxygen exchange ceases as the dissociation of oxygen at low temperatures is negligible. The limb may solidify completely. This is followed by a period of vasodilatation signified by a return of a pink color to the limb. Then the familiar white cadaverous appearance sets in as final vasoconstriction and vascular stasis takes place.

With the commencement of thawing, the limb becomes intensely red, hot and swollen. The red blood cells assume their discreteness as the capillary flow increases and vascular engorgement occurs. Increased capillary permeability leads to diffusion of plasma into the interstitial spaces and the red cells now silt up the capillaries to form sludges known as "agglutinative thrombi." Within twenty-four hours these are well formed but can easily be washed out or resolved. After forty-eight to seventy-two hours, however, actual hyalin thrombi are observed. Following the development of edema, blebs or bullae are formed. These contain straw-colored or blood-tinged fluid whose protein content is similar to that of plasma. Within twenty-four to forty-eight hours, fibrin is deposited in the blisters which is probably accompanied by a similar phenomenon in the interstitial spaces after the exudation of plasma. This is followed by fibrosis and scarring and hence the subsequent oft times irreparable damage to the tissues and nerves. Thus, the loss of sensation to moderate pain and temperature. After seventy-two hours and within ten days, the black areas of gangrene appear as a result of vascular occlusion by the hyalin thrombi previously mentioned. Obviously the degree of gangrene will depend on the extent of thrombotic involvement and resultant impairment of circulation.

It was with this basic pathology in mind that heparin was introduced as a prophylactic drug in the treatment of frostbite. Early heparinization prevented tissue loss in experimental animals exposed to cold; untreated rabbits' legs exposed to cold developed necrosis and gangrene. Optimum results were obtained when treatment with heparin was commenced immediately after thawing. It has been shown that the coagulation time must be kept continuously well elevated, in order to avoid the peaks and valleys accompanying intermittent, fractional heparin therapy. It is thought that the heparin acts not on the initial red blood cell collections during freezing (when plasma still remains), but on the agglutinative thrombi by overcoming the acquired reversible adhesiveness of the erythrocytes. Moreover, the heparin was found to preserve the resorbability of the interstitial fluid, thus preventing secondary fibrous tissue formation. It was shown that in heparinized subjects there was, likewise, no clot formation in the blisters occurring during the thawing period.

The practicability of a large scale heparin program for frostbite was proven by Lange and Loewe. This investigation had a two fold purpose: first, to corrorborate animal experiments and, second, to evolve a single, practical method for the heparin treatment of frostbite. The repository heparin preparation (heparin in a retarding gelatin-dextrose menstruum) developed by Loewe et al for treatment of thromboembolic disease seemed uniquely applicable in this connection. The intravenous administration of the aqueous commercial preparation of heparin especially under battle conditions, would obviously prove impractical, if not impossible. The method of depositing heparin intramuscularly or subcutaneously in a retarding gel achieves a consistent, sustained and equable release of the anticoagu-

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lant. The ability to predictably induce effective high level, continuous and uninterrputed anticoagulant effects with these preparations is, as already indicated, of distinct advantage in the heparin therapy of frostbite.

The practical demonstration of the therapeutic value of the method was made possible by a study of artificial frostbite in human volunteers. In one group the frostbite was accomplished by means of a porcelean crucible filled with dry ice and applied, without pressure, to the skin of the lateral aspect of the upper arm for ten minutes. An area about 2 centimeters in diameter came in contact with the skin. By this method a temperature of approximately minus 22 degrees C. was achieved. Heparinization was started immediately following the exposure. One volunteer served as a control. The other group was subjected to local refrigeration in the same manner but for two exposures of 30 minutes each. The initial or control exposure was permitted to develop for six days before the second frostbite was induced, immediately following which, treatment with repository heparin was initiated. The thirty minute exposure with dry ice results in temperatures considerably below minus 22 degrees C., and is comparable, as to the degree of exposure. to the frostbite suffered by aviators in high altitude flying such as nose gunners after demolition of the plexiglass protection or gunners attempting to unjam guns without glove protection.

The metamorphosis of the untreated lesions and the repair following heparin therapy demonstrated not only the effectiveness of heparin, but the necessity for early administration and continuous and adequate therapy.

Some investigators have taken an entirely different approach to the problem of pathogenese of cold injuries. A brief discussion of their concepts and consequent bearing on therapy is in order.

It is apropos to state that at times, immersion foot has been confused with frostbite. The two conditions, while they may coexist, are dissimilar clinically and pathologically; the therapy must perforce differ. Immersion foot is primarily a neuromuscular disorder; vascular changes due to "agglutinative phenomena" are absent unless there is complicating cold injury. The functional pathology is predicated on anoxemia and a depressed metabolism; characteristically edema appears concomitantly with the development of immersion foot despite an intact circulation. Contrariwise, in frostbite the edema appears only after thawing and, of course, the gangrene which supervenes in the untreated case is a reflection of primary vascular injury. The fluorescein technique serves as a valuable diagnostic aid in the differentiation of these two pathologic companions.

Lewis, studying rabbits' legs exposed to cold, believes that progressive necrosis of muscle and connective tissue occurs within fifteen to thirty minutes after exposure. Friedman has been unable to repeat this work. The edema which occurs in muscles four to six hours after exposure is claimed not to be due to ischemia because muscles rendered totally ischemic by tight tourniquets for forty-five to ninety minutes did not show any changes. Lewis demonstrated that although the blood vessels were dilated and engorged, no thrombi appeared before twenty-four hours. By this time muscle degeneration was well established. He, therefore, deduced that muscle necrosis was due not to vascular changes, but rather to the direct action of cold on the tissues, i.e. thermal injury. If this be true, then thrombosis is not the basic cause of gangrene, but rather merely evidence of thermal injury to the blood vessels per se. Lewis reasons that the action of cold on the blood ves-

sels occurs not as a selective but as a generalized action on all tissues. As previously stated, Kreyberg, Lange, et al dispute this postulate, claiming that tissue necrosis is secondary to red cell sludge formation occurring in the capillaries promptly after thawing. Lewis, while insisting that vascular changes may play some role in the gangrene of frostbite, questions that rationale of anticoagulant therapy because it has yet to be proven beyond doubt whether vasodilatation with edema or ischemia from vasoconstriction or both are the deleterious factors even in the absence of thrombotic complications.

Apart from the debate over the role of anticoagulant therapy in the prevention of gangrene in frostbite, there has been much controversy regarding the manner of thawing particularly with respect to the influence of temperature. Until recently it was thought that either heat or cold was detrimental and added to the extent of tissue necrosis. However, Shumacker and his group have shown that the incidence and extent of gangrene was not dependent upon the continuance of the frozen state per se, but rather on the extent of the area frozen, the degree and persistance of the vasoconstriction induced and the completeness and duration of the resulting capillary stasis. They feel that rapid thawing at 42 degrees C. is effective because (1) it decreases the duration of the frozen state, (2) tissues tolerate poorly near freezing temperatures, (3) there is better physico-chemical restitution of cells than in the case of slow transition, and (4) by decreasing the duration of vasoconstriction, prompt vasodilatation inhibits stasis and thrombosis and so provides blood to anoxic tissues. These premises are supported as well by Pinchotka and Lewis. The Russian investigators also accept the principle of rapid rewarming. Their concept is that actual freezing of the tissues cannot occur until after death. The decisive factor in frostbite is rather the period of exposure at low but not freezing temperatures. Actually, a frostbitten member cannot be warmed quickly because of the inherent low temperature. However, the more rapid the thawing, the less the necrosis and degeneration.

It might be well to mention a few additional forms of therapy before recommending an integrated therapeutic program. Both Crismon and Ungley believing that the edema is an important phase of the subsequent tissue necrosis, directed their treatment towards reducing swelling by pressure bandages and counteracting deficient oxygen supply by decreasing local tissue metabolism through the slow thawing method. Ice packs have been advocated to diminish the number of blisters during thawing. While this did decrease the pain and exudation at the time of application, removal of the cold packs was followed by a violent eruption of bullae and excruciating pain in the affected part. Various types of plaster casts have been applied even prior to the swelling. Shumacker demonstrated that this method is of no value and that there is no relation between the extent of gangrene and the amount of edema. The same investigator found that rutin and benadryl did exert some palliative effect in frostbite. The rutin, perhaps, by increasing the tone of the capillaries might delay the onset of stasis and extravasation of serum. If it be assumed that a histamine-like substance might be responsible for the capillary damage and subsequent stasis and thrombosis, then anti-histamines such as benadryl would be of value in preventing blood vessel injury.

Theoretically, cortisone should be reserved for those cases accompanied by severe shock. As a routine measure, its reputed tendency towards increasing blood coagulation might be a detrimental factor.

Many other drugs and methods of

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treatment have been tried without too much success. Doubtless much will be added to the therapeutic armamentarium as the investigation in the field of frostbite continues. At present, however, the therapy should embody those facts which are indisputable.

The practical treatment of frostbite may be divided into three phases, (1) prophylaxis, (2) early treatment of afflicted individuals up to seventy-two hours after exposure and (3) late treatment to provide symptomatic relief after irreparable damage has ensued. For purposes of prevention, all individuals who might be called upon to engage in activities subjecting them to exposure to severe cold should be tested for impaired circulation. Physical examination would thereby exclude those with diabetes, advanced arteriosclerosis, Buerger's disease, vasomotor instablity, luetic arterial disease, foot deformities, malnutrition, post-traumatic circulatory disorders, etc. Persons subject to epilepsy, alcoholism and myocardial insufficiency are similarly poor risks. Subjects with a history of physical allergy should be screened.

Properly fitting warm clothing and footwear are mandatory. There should be no constriction and socks should be changed when wet as moisture accelerates the dissipation of heat from the body. Rubber boots are contraindicated as they increase the tendency to perspire. Whereas oil or greases may afford some protection for a limited time, the Russian investigators found that they were harmful after prolonged exposure. It is more important to keep the extremities dry in order to preserve the natural skin oils. It should be emphasized that prolonged dependency of the extremities, the assumption of a cramped position and the constriction by tight or wet clothing by compromising the peripheral circulation all predispose to frostbite. Gentle massage of the hands and feet before numbness and tingling set in may be of value. Actually the Russians advocate gentle message even after frostbite has occurred as they insist that the affected part is no more fragile than normal tissue. Elevation of the affected part is advisable to prevent venous stasis.

Once frostbite has actually occurred, the necessity for prompt and intensive treatment including optimal anticoagulant therapy cannot be overemphasized. Theis and O'Connor have reported excellent results with a very rational and intensive treatment program. In a series of thirty patients in various stages of frostbite, only one of the fourteen treated with anticoagulants suffered any loss of tissue and that one merely the amputation of a finger. The treatment program should be directed toward the prevention of shock, infection and intravascular clotting. All too frequently the patient may have been exposed to the elements for long periods of time following unconsciousness from alcoholism, cardiac or cerebral accidents, trauma or coma. The patient should be observed for shock by frequent blood pressure, pulse and respiratory readings as well as the laboratory adjuncts of blood counts, hematocrit and electrolytic studies. If shock is imminent, sedation, oxygen, plasma, etc. should be utilized. Pressure bandages should be applied to the legs and kept for ten to twelve days. Surgical asepsis should be observed. Any wounds should be cleansed and dressed with dry or petrolatum gauze. Anti-tetanus treatment should be instituted if need be, and of course, appropriate antibiotics may be employed where indicated. In this connection, it would be well to remember that many antibiotics tend to increase the clotting tendency. Thawing should take place relatively rapidly. Recent work by Schumacker and Lewis as well as

the Russians have shown that rapid thawing will save some tissue and shorten the time of disability. It is claimed that most tissue damage occurs not at freezing, but at low temperature during the act of thawing. Shumacker goes so far as to advocate thawing at 42 degrees C. Most investigators now agree that room temperature or somewhat higher is desirable.

For best results, if possible, anticoagulant treatment should be introduced immediately or within twelve hours after the start of thawing. Good results may be expected if begun up to twenty-four hours. Moreover, since actual hyaline thrombi are not seen until seventy-two hours following thawing, a vigorous program, even then, might be of inestimable value. Although intravenous heparin was first used in order to obtain a rapid and continuous elevation of the clotting time, such a regime would be both expensive and cumbersome. Particularly in combat where such procedures could not readily be carried on in the forward echelons, a more practical form of anticoagulant therapy would be needed. The subcutaneous or intramuscular deposit of repository heparin gel (heparin in a retarding gelatin-dextrose menstruum*) has been demonstrated to serve this purpose admirably. The availability, ease of transport and administration, predictability of action and relative simplicity in following its effects make it the anticoagulant method of choice. Four hundred mgms daily for five consecutive days following exposure will give a constant, effective and continuously elevated coagulation time with prevention of intravascular clotting; a five day span of therapy is sufficient. The urgency for prompt and adequate anticoagulant therapy should be emphasized; after seventy-two hours it is of little or no avail. Dicumarol while cheaper to administer requires a complicated technique for control, is unpredictable in its action, has been shown to have a deleterious effect on blood vessels themselves and cannot be depended upon to maintain a constantly elevated prothrombin time without the concurrent danger of hemorrhage. Moreover, in frostbite the most critical period is twenty-four to forty-eight hour lag in its effect would not be of any avail. Obviously the use of dicumarol per se would lead to treatment failure. Heparin, because of its prompt action, absence of side effects, and ease of control, is undoubtedly the anticoagulant of choice in frostbite.

For adjunctive therapy papaverine hydrochloride 60 mg. intravenously or 300 mg. intramuscularly every four hours, as well as 100 mg. of nicotinamide twice daily might be used to induce collateral vasodilatation. Paravertebral nerve block or sympathectomy have not been shown to be of value in actual frostbite.

Once the actual tissue damage has been established, treatment becomes completely palliative and supportive in nature. If a level of gangrene develops, amputation is indicated in order to save life. Arteriography may be considered to outline the extent of vascular involvement. Appropriate antibiotic measures should be employed. In cases with severe vasomotor and neurological symptoms such as numbness, tingling, coldness, etc., sympathectomy or paravertebral blocks may be of some value. Parenthetically, although there may be complete restitution of circulation with avoidance of loss of tissue, nerve injury may be permanent. Residual neurological symptoms, such as causalgic states, are rather common. The result of this final stage is, of course, deplorable. Some degree of amputation is the usual outcome and the residual neurological and vasomotor symptoms become a major concern. The tragic consequences then, in this last stage of frostbite, should emphasize the

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need for scrupulous adherence to the measures outlined in phases 1 and 2, namely prophylaxis and prompt judicious treatment following exposure.

In summary, we have outlined the pathogenesis and treatment of frostbite. The two major views relative to the basic functional pathology are presented. On the assumption that the theory of intravascular clotting is most plausible, the utilization of repository heparin is discussed along with corroborative evidence as to its value in the prevention of gangrene following frostbite. A detailed therapeutic program is proposed emphasizing primarily the necessity for rapid thawing and a properly conducted anticoagulant regime.

•Repository Heparin, Lederle Laboratories, Division American Cyanamid Company. Heparin Pitkin Menstruum, William R. Warner. Depo Heparin, Upjohn Company.

Cerebral Concussion

SAMUEL ROSNER, M.D., F.I.C.S.

Cerebral Concussion and its aftermath the Post-Concussional Syndrome have become the problems of all who are interested in clinical medicine. The neurologist and the psychiatrist are completely confounded by a problem, which in severe cases, does not lend itself to solution by either one. The neurosurgeon is only slightly more fortunate. He can indulge in spinal taps and pneumo-encephalography before deciding that the case is usually hopeless. However, the problem lends itself to attack and solution from a physiological viewpoint.

Cerebral Concussion should be defined as a condition caused by a direct or indirect trauma, to the head, the trauma being of sufficient force to cause momentary dizziness. Cerebral Concussion may in extreme cases, be accompanied by brain injury, or intra-cranial hemorrhage or both. These conditions may be accompanied by loss of consciousness, but that is not always the case.

It is necessary to understand that loss of consciousness does not invariably result from head injury which is severe enough to cause "Commotio Cerebri." This type of traumatized brain when viewed at craniotomy is slate gray in color. There is very little cerebro-spinal fluid in the sub-arachnoid space. The cortex is oedematous and usually non-pulsating. One finds that it is more friable than usual. There is no doubt that the brain in the post-concussional state is no longer in physiological equilibrium.

The patient will give a history of direct or indirect blow to the head. There may be, subsequent nausea and vomiting. The vomiting will usually occur within the first twenty-four hours. Nausea usually accompanies the headaches. Although, the headache may not be accompanied by nausea or vomiting, even in the most severe cases.

The patient upon being struck usually falls to the ground, upon recovering from the blow and getting to his feet, he will be dizzy and may

vomit. In many cases, the patient will not vomit until he reaches hospital, or home.

Immediate examination reveals some significant signs. The patient is pale, dizzy and invariably exhibits hypotension. His dizziness will increase with change of position of his head, expecially if he is asked to put his head down toward his knees. Asking the patient to tie or untie his shoe laces will always bring on the dizziness, and his face will become either abnormally pale, or abnormally flushed.

After a few hours, or a few days, the concussed patient begins to complain of severe headache, as well as dizziness. The headache is usually constant but may vary in severity, becoming almost unbearable at times. Medication may relieve the headache but not for long. The headache may be generalized or local. If there is local headache which is constant in situation, then subdural hematoma should be suspected.

The patient may improve with time, what usually happens is the partial improvement of headaches both in frequency and severity. However, other symptoms make themselves known. The most common are complaints referable to the eyes. These may be "pain behind the eyes," "spots in front of the eyes," "blurred vision" or distortion of objects.

There is one constant sign that will help in distinguishing the neurotic from the organic injury. The person who really suffers from post-concussional headaches has a constant hypotension. In 112 cases for post-concussional complaints, hypotension was found in 96 cases. We define hypotension as a systolic pressure of 115 mm of Hg, or less. 82 patients had a systolic pressure of 110 mm of Hg, or less. The remaining sixteen patients may have been suffering from a neurosis, but since we did not have any record of blood pressure previous to the accident, the patient's statements were given due consideration. Hypotension, may be relative. That is, if a patient suffering from a post-concussional syndrome has a systolic pressure of 140 mm of Hg, when he formerly had 165 mm of Hg, then we consider that he is suffering from a relative hypotension.

Hypotension has been such a constant sign in the post-concussional syndrome that I have come to consider it pathognomonic of the condition and never consider the patient a neurotic or malingerer who exhibits this sign. That is, I consider that the patient is suffering from definite organic brain changes.

The neurotic patient, while he is deserving of consideration as the organic injury is the problem of the psychiatrist.

There are two possibilities which should be thoroughly investigated in every head injury. They are brain damage, intra-cranial hemorrhage or both. Chronic subdural hemorrhage is the condition that is most often missed in head injuries.

Investigation of the problem consists of thorough neurological examination, skull X-rays, electro-encephalography, spinal tap, with the investigation of the cerebro-spinal fluid, and occasionally pneumo-encephalography.

In the neurological examination special attention should be given to the examination of the pupils and eyegrounds. If the pupils are unequal, in size, or if they react to light unequally, or if the eyegrounds show congestion or edema, then the patient should undergo spinal tap with menometry and complete examination of the cerebro-spinal fluid, electro-encephalography should be performed and pneumo-encephalograph taken.

Subdural hematoma is the most common chronic condition resulting from head trauma, except for the ordinary post-concussional state. We

will try to picture the findings upon investigation of such a case.

The patient complains of headache, dizziness, and lapse of memory. Usually, a member of the family will volunteer the information concerning partial loss of memory, change in personal habits, and general personality degeneration to some degree. The eyes will show sluggish reaction in one, or both pupils. There may be a difference in the size of the pupils. If this condition persists, then it is almost certain there is a subdural hematoma present. The chronic clot will be liquified and will be found on the side of the most sluggish pupil. Bilateral chronic subdural clot is comparatively rare in my experience. The patient will show a relative hypotension but there may be an increase in pulse pressure with it. There may be slightly diminished motor power with the corroborating signs of an upper motor neurone lesion. The muscle weakness may be in the face, upper or lower limb, or all three. Spinal tap may show an increase in fluid pressure. This is not necessary to corroborate the diagnosis. Protein may be slightly above normal. Some red cells may be found in the cerebro-spinal fluid However, the findings may be normal.

Skull X-rays usually show nothing of significance unless air is injected into the subarachnoid space and ventricles. This can be done by lumbar or cysternal puncture. About 80 c.c. of C.S.F. are withdrawn in 10 c.c. portions. Each 10 c.c.'s of cerebro-spinal fluid are replaced by 10 c.c.'s of air. Upon attaining adequate filling of the ventricles and the subarachnoid space, definite conclusions can be drawn from the roentgenograms. Shift of one, or both, ventricles in the same direction, distortion of one or both ventricles, or a Dyke's line[1] in the subarachnoid space confirm the diagnosis of intracranial pathology. The Dyke's line if definite is the only sign in the pneumo-encephalogram that is pathognamonie of t subdural cyst. Ventricular distortion or shift may also be found with intra-cranial neoplasm. In cases of long standing calcium may be laid down in the wall of the clot.

Subdural hydroma which seems to be no different in chemical content than cerebro-spinal fluid, may result from a tear in the arachnoid membrane. This collection of fluid in the subdural space will act like a subdural clot, clinically and roentgenologically. Release of the fluid results in cure of the patient's complaints.

The electro-encephalogram in chronic subdural clot is useful both in localization and lateralization of 80% of subdural hematomas.[2] Usually, the electro-encephalogram in brain trauma shows slow improvement. In subdural hematoma the clot acts as a tumor and delta waves persist.

In mild head injury,[3] with only a short period of unconsciousness, the electro-encephalogram may be normal if taken one week, or more, after the injury. A normal record, in the absence of clinical signs, usually indicates a good prognosis for complete recovery. However, an abnormal E.E.G. in the absence of clinical signs usually carries with it a bad prognosis. The electro-encephalogram should be repeated at regular intervals to see whether improvement is taking place.

Treatment of cerebral concussion consists of immediate care, and care of the prolonged or post-concussional syndrome. Whether the patient is sen in hospital, or in the physician's office, the patient with a recent head injury should be put to bed. This should be done even if clinical examination and skull X-rays are negative. Mild sedation T.I.D. and large doses of Vit. B_1 should be given daily. The Vitamin B_1 should be

given intravenously, slowly in doses of 300 mgm. If after two days in bed, the patient still feels well and insists upon resuming his normal life, he may be allowed to do so.

The patient who vomits, complains of headaches and is obviously upset by his accident and yet shows no clinical signs should be kept in bed for 10 days. Sedation should be mild and given three times daily and a good night's rest should be assured by sedation before sleeping time. A daily intravenous solution is to be given consisting of 15 c.c. of ethyl alcohol 80 to 95% and 500 mgm Vitamin B_1 in 500 c.c. 5% glucose-saline. This solution should be run into the vein within 60 minutes. The patient should be allowed to go to the bathroom but not allowed out of bed for any other purpose, during the first ten days. His diet should be soft and he should receive a mild purgative if bowel evacuations are not regular. After the tenth day, the intravenous solution may be discontinued, the patient be put on a regular diet and he be allowed the freedom of the ward. By the end of the fourteenth day, he can be discharged.

This two week treatment can also be applied with great benefit to the patient who is suffering from a post-concussional syndrome for many years. I have found that the daily, intravenous infusions of Ethyl alcohol and Vitamin B_1 in 5% glucose-saline have been extremely efficacious even in the most obstinate cases. Of twenty-one cases, only two cases needed a second course of treatment, the other nineteen were completely rehabilitated and returned to their jobs and had no complaints except for an occasional headache.

In conclusion, it must be said, that this routine of treatment has proved to be successful and in no case harmful. Since, to my knowledge, no adequate treatment has ever been proposed for the patients suffering from post-concussional after-effects, it would be worthwhile for physicians dealing with this type of case to try it. In every case, except the mildest, complete neurological examination, skull and cervical spinal X-rays, spinal puncture with examination of cerebro-spinal fluid and electro-encephalography should be performed. Pneumo-encephalography should be done without hesitation if the clinical signs, or electro-encephalograms, or both, indicate persistant brain involvement. If all tests are negative and the patient persists in his complaints then he should be given the benefit of the treatment outlined in this paper. It should be kept in mind, that the true post-concussive suffers from hypotension while the neurotic does not. This is a valuable means of differentiating the two types.

1. Davidoff, L. M., and Epstein, B. S.,—The abnormal Pneumo-encephalogram—Lea &Febiger 1950
2. Sullivan, J. F. — Abbot, J. S.,—E.E.G. in casen of Subdural Haematoma Proc. E.E.G. Clin. Neurophysiology 1:517, 1949
3. Electro-encephalography in Clinical Practice—Robert S. Schwab—Saunders Co. 1951

SIDE-GLANCES at HISTORY OF MEDICINE

HAY FEVER

The first accurate description was given by J. Bostock (A Case of a Physical Affection of the Eyes and Chest. Chir. Tr., London, 10:161, 14:437, 1819). Pollen of ragweed as the main cause of "autumnal catarrh" was discovered by Morrill Wyman (1812-1903) and described as "autumnal catarrh" in 1872. The first physician, however, who thought of pollen as etiological factor of hay fever was J. Elliotson (Hay Fever—Information Solicited. London M. Gaz. 8:411, June 25, 1831).

Gastrointestinal-Cardiac Relationship

There are four ways in which abdominal organs may adversely influence the cariovascular system: 1) sudden increase in reflex vagatonia with consequent embarassment of coronary circulation; 2) abdominal distention or acute dilation of the stomach or a large diaphragmatic hernia serve to diminish the vital capacity of the lung and also may interfere with the motion of the heart; 3) effect of electrolyte change occurring in intestinal obstruction, removal of ascitic fluid and pancreatitis is reflected in alterations of th EKG; 4) shock producing states such as hemorrhage from peptic ulcer or shock from fulminating peritonitis may sepress cardiac function. (E. Suckle and G. K. Wharton. The Am. J. of Dig. Dis. 9:261, September 1951).

Cold Waves

The introduction of the cold permanent wave processes has created the most recent hazard. Patch tests were done on 223 subjects with both thioglycerol and thioglycolate lotions. 20 reactions were observed to thioglycerol lotion and 24 to the ammomium thioglycolate lotion. Eight subjects reacted to both lotions. Retested were 213 subjects. 76 reactions to thioglycerol occurred; 36 were immediate, 7 were immediate followed by delayed, and 33 were delayed reactions. There were 26 reactions to ammonium thioglycolate 25 being immediate and 1 immediate followed by a delayed reaction. 16 subjects reacted to both lotions. The delayed reactions occurred 6 to 9 days after the patches were applied. Both solutions have an irritating plus a sensitizing action. (J. G. Downing. Arch. of Dermat. & Syhilol., 63:561, May 1951).

Sheehan's Disease

(Postpartum Necrosis of Anterior Pituitary Gland)

Incidence about 9 (2 severe) in each 10,000 population. Hemorrhage and collapse during delivery are the causes of ischemic necrosis of the adenohypophysis. Clinical features depend on extent of pituitary destruction. Inhibition of lactation after complicated delivery may be the only finding. In well developed cases there are: amnorrhea (without menopausal symptoms); loss of sexual function (atrophy of ovaries, superinvolution of uterus, atrophy of vagina, scantiness of pubic and axillary hair, atrophy of breasts); asthenia; somnolence; mental and psychic changes; intolerance to cold; occasionally headache; waxy pallor of skin. Blood sugar is invariably low (hypoglycemic attacks). Urinary gonadotropins are depressed. Some patients die of intercurrent infections, most die in coma. (J. E. Cook; Wm. B. Bean; M. Franklin and J. F. Embick. Arch. Int. Med. 4:517, April 1951).

Acanthosis Nigricans

Is characterized by appearance of plaques in cutaneous folds (axillas, genitalia, perianal region, umbilicus, mouth angles). Hyperkeratosis of palms and soles may be present. The juvenile type appearing early at life or at puberty is generally, yet not always benign; the adult form, after age 40, is frequently associated with abdominal malignancies, but also with cancers of uterus, ovary, breast, lung and mediastinum. Onset of cutaneous lesions and tumor is often concomitant, or the skin manifestations precede the diagnosis of the neoplasm by several months (M. Berke and F. B. Wilkins, Ann. Surg. 132: 980, November 1950).

Postoperative Ambulation

Thrombophlebitis has not been reduced by early ambulation. However, the percentage of deaths due to pulmonary emboli, in authors' series, showed a reduction: 17.1% in the ambulatory group compared with 28.5% in the control group. Pulmonary complications were reduced to a gratifying extent. Pneumonia was reduced by 2% and atelactasis by 1%. The total reduction in pulmonary complications was about 3.3%. The total morbidity was reduced by 5.4%; i.g. cystitis was reuced by about 50%, while the incidence of postoperative peritonitis showed only a reduction of 0.28%. (E. Todd, Jr. and F. M. Massie. The J. of the Kentucky State Med. Ass. 9:401, September 1951).

Tuberculosis of Appendix

Primary tuberculosis of the appendix is very rare. The initial symptoms are indefinite. There is loss of appetite, irritability of the gastrointestinal tract with nausea, possible vomiting and moderate loss of weight. The patient may have alternating attacks of diarrhea and constipation. Later diarrhea attacks become more frequent and are associated with foul smelling stool. Colicky pains are also present in the lower half of the abdomen. Physical examination only reveals slight tenderness on deep palpation in the lower right quadrant. In the differential diagnosis nonspecific appendicitus, granuolomas and neoplasm of the gastrointestinal tract and even peptic ulcers have to be considered. One case is reported in which the diagnosis was made microscopically after operation. The appendix was removed and dihydrostreptomycin was continued for four months after surgery in ½ gram doses twice daily. (T. M. Larkowski and A. R. Rosanova. The Illinois Medical J., 4:265, October 1951)

Pleuropericardial or Pleurocoelomic Cyst

A thin-walled structure occupying the right cardiophrenic angle. It is covered by pleura and lined by endothelial-like cells. The cyst fluid has a low specific gravity, low protein content and has few, if any leucocytes. Relatively few cases have been reported in the literature although there is evidence that they must occur fairly frequently. In tuberculosis surveys they might be often seen; this will require careful differential diagnosis to separate this relatively innocuous cyst from similar-appearing tumors of the chest. Roentgenologic examination and, in selected cases, aspiration, may give conclusive evidence. (K. M. Lippert; H. Potiky and I. K. Furman. Arch. Int. Med. 3:378, September 1951).

Achylia Gastrica

"Achylia gastrica and achlorhydria are not synonymous. Achlorhydria is lack of free hydrochloric acid, a symptom found secondarily in many diseases and conditions, of no clinical significance. Achylia gastrica is complete absence of gastric juice, primary and constitutional. The differentiation is of greatest importance because achylia gastrica—not achlorhydria—leads to pernicious anemia. The entity of achylia gastrica shows three strictly circumscribed signs: 1) absolute lack of gastric juice; 2) disturbance of chymification; 3) disturbance of motility. These three signs, necessary for the diagnosis of achylia gastrica, can be determined only by the Boas-Ewald test meal. . . . Achylia gastrica is not based on gastritis atrophicans. It can exist with normal gastric mucosa. . . . Achylia gastrica is unchangeable. The development of achylia gastrica has never been observed. . . There is a familial occurrence of achylia gastrica." (F. S. Weinberg. Am. J. Dig. Dis. 12:351, Dec. 1951).

THERAPEUTIC SUGGESTIONS

Angina Pectoris

As the anatomical basis in the majority of cases is narrowing and occlusion of arteriosclerotic coronary arteries one of the main objectives of treatment is artificial dilatation of the collateral circulation by drugs or other therapeutic procedures. The myocardium becomes painful when it is forced to work without adequate blood supply. Thus, a second objective of treatment is to eliminate all factors which would decrease the 'coronary reserve' (Difference between the amount of work performed by the resting heart and the amount necessary to induce pain). Physical activity should stop before pain appears; yet, muscular activity which does not induce distress should be encouraged. Emotion may rival physical exertion in producing pain. The main anchor of medicinal therapy is still nitroglycerin. It relieves pain almost invariably within a minute, and patients do not develop tolerance for it. Its effect lasts from 10 to 30 minutes; it may be repeated many times a day; the usual dose is 1/100 grain; headache and lightheadedness are frequent side-effects, which would make necessary diminution of the dosis. Khellin was introduced in 1946. Clinical reports are conflicting but it has been effective in many cases. As it is a gastric irritant, adequate dosage is often made impossible. Angina decubitus is a complication which may be improved by mercurial diuretics. After meals a rest period of 20-30 minutes is imperative. Smoking should be restricted. Air travel is tolerated as long as the altitude does not exceed 8,000 feet. Lowering the basal metabolic rate by destruction of thyroid tissue by use of radioactive iodine may have a therapeutic future. (J. H. Palmer. Cand. M.A.J., 65:207, Sept. 1951).

Superficial Carcinomas

Superficial or accessible cancers (located in skin, mouth, larynx, and cervix uteri) are quite sensitive to ionizing rays and may be destroyed with but a minimum of damage to adjacent structures. Radium provides the ideal modality in the treatment of these growths. With present-day tables the exact dose delivered at any point distant from the radium applicator can be accurately calculated. Cancer cells are usually killed with half the dosage required to kill normal cells. With all types of ionizing radiation this differential is increased if the dose is fractionated and spread over a period of 3 or 4 weeks. Radium gives off 2 types of rays: beta rays which are powerful but do not penetrate deeply, and gamma ray which penetrate tissue easily. Cancer of the skin, lip, tongue, lining of the mouth, pharynx and larynx are ideal sites for the use of radium. Cancer of the cervix also is best treated by radium. The tissues of the vagina and uterus will tolerate several times the dosage that other normal tissues will stand. This permits a carcinomacidal dosis to be administered at some distance from the vagina itself. Cancers of the lip if treated with radium should recover unless they are very extensive, unless they have already spread to distant areas, or unless the tumor is unusually radio-resistant. Cancer of the tongue presents a more difficult problem, but as a rule responds satisfactorily to treatment if not too extensive. Cancers of the mucous membranes of the mouth usually recover under radium treatment unless the growth is very large or unless it lies against the bone. (J. Ernest Breed. Ins. Med., October-November 1951, p. 97).

Books on Neurology

A painstaking, critical and thorough description of the human isocortex gives an excellent insight into the structure of the main part of the CNS.[1] The practitioner will be most interested in the last chapter which deals with functional significance. Very instructive plates and an extensive bibliography are helpful tools in understanding this not always easily written book. Prevention of poliomyelitis by diet is a contention[2] which is the author's individual opinion. More evidence will be necessary before this view could be accepted. A model description of ways and means to rehabilitate cerebral palsy patients[3] will be a help to all physicians concerned with such cases in their communities. The excellent textbook of neurology[4] by Dr. Brain appears in its fourth edition. The book has been integrated by addition of several subjects which have come into the foreground since the previous edition four years ago; streptomycin treatment in tuberculous meningitis, vitamin B_{12} in combined degeneration; sections on temporal arteritis, infectious mononucleosis, sarcoidosis, etc. The book is a very clearly composed, comprehensive survey of all neurological problems. European viewpoints are predominant, yet American publications are frequently referred to. A particularly profound discussion on nerve impulse[5] is the topic of the second conference. The problems involved have aroused wide interest in recent years because of their importance not only in physiology but also in neurology and psychiatry.

1. The Isocortex of Man by Percival Bailey, M.D. and Gerhardt von Bonin, M.D., Urbana, 1951, The University of Illinois Press. 301 pages. Cloth (no price)
2. Diet Prevents Polio by Benjamin P. Sandler, M.D. 1951, The Lee Foundation for Nutritional Research. Milwaukee, Wisc., 82 pages. Cloth. (no price)
3. Cerebral Palsy Service. Report on Cerebral Palsy Study conducted by Chicago Metropolitan Unit. Illinois Association for the Crippled. Not paged. No. 3.
4. Diseases of the Nervous System by W. Russell Brain, M.D. Oxford University Press, New York-London, 1951. Fourth Edition. 1002 pages. Cloth. $8.50.
5. Nerve Impulse. Transactions of the Second Conference, March 1-2, 1951. Editor, David Nachmansohn, M.D. Josiah Macy, Jr., Foundation, New York, 1951. 204 pages. Cloth. $3.50.

Books on Internal Medicine

Growth[1] in its physiological and pathological implications is one of the most important subjects of medicine; the chemical and physiological aspects are instructively presented by 10 experts under the editorship of A. K. Parpart. A judicious introduction into the disorders of the cardiovascular system[2] has been prepared by J. C. Bramwell. The book only gives a basis for later clinical experiences and is directed to the senior medical student. A very useful little volume deals with the essential topic of cardiac pain[3]. Particularly enlightening is the section on the differential diagnosis of chest pain. The surgical therapeutic outlook and the description of local block are also arresting chapters. In the same series of books we find a very lucid exposition of the pharmacological aspects of heart disease[4]. This short sketch is of great practical value. A very impressive work is the establishing of normal electro-

cardiographic patterns (all leads) of children between the ages 0 to 16[5]. The atlas displays the characteristic electrocardiograms. The book is enriched by a statistical study. This book will be of great assistance to the practitioner as it shows forth the standard patterns on the basis on which pathological potentials easily can be recognized. A book to be highly recommended is the 7th edition of Rosenau's Preventive Medicine. The scope of this well known treatise has required again a revision in which many experts in the field collaborated. Some chapters, particularly those on communicable diseases and maintenance of health afford a wealth of information for the general practitioner.

1) The Chemistry and Physiology of Growth. Edited by Arthur K. Parpart. Princeton University Press, Princeton, N. J. 1949. 293 pages. Cloth. $4.50.

2) The Approach to Cardiology, by J. Crighton Bramwell, M.D. Oxford University Press, New York, 1951. 122 pages. Cloth. $3.75.

3) Cardiac Pain, by Seymour H. Rinzler, M.D. Charles C. Thomas, Publisher, Springfield, Ill., 1951. 139 pages. Cloth. $2.50.

4) Pharmacology of the Failing Human Heart, by John McMichael, M.D. Charles C. Thomas, Publisher, Springfield, Ill., 1950. 63 pages. Cloth. $2.

5) Electrocardiographic Studies in Normal Infants and Children, by Robert F. Ziegler, M.D. 195 pages. Cloth. Charles C. Thomas, Publisher, Springfield, Ill., 1951. $10.50.

5) Rosenau Preventive Medicine and Hygiene, by Kenneth F. Macy, M.D. Seventh Edition. Appleton-Century-Crofts, Inc. New York, 1951. 1462 pages. Cloth. (Price not given)

Books on Gynecology and Surgery

Amenorrhea[1] is frequently a vexing problem for the general practitioner. Diagnostically, it remains the main task to determine whether amenorrhea is a sign or symptom of a systemic or local disease, whether it is a primary condition when the patient never has experienced menstruation or a secondary one when menstruation has preceded amenorrhea. According to the importance of the etiological causes the treatment is flexible and varying; consistently, the major part of the presentation is concerned with therapeutic measures. An exceedingly timely book, reflecting great experience, deals with injuries to the extremities[2] in military medicine. While the general surgical procedures are not essentially different from those in civilian surgery, the adjustment to the environmental conditions of combat zone, transportation, first aid and emergency necessities requires a specific type and timing of surgical therapy; this holds true also of special types of injuries. This book, in the lucidity of its exposition is to be highly recommended. The practical application of anatomy for the practitioner is closely connected with surgery and gynecology. Thus, the new 9th edition of Cunningham's textbook[3] may consistently be mentioned here. It has been judiciously edited by Dr. Brash and is one of the most comprehensive and up-to-date anatomical presentations. An almost indispensable book for the physician with surgical practice is a volume[4] which describes minutely the care of the surgical patient: the surgical risk, the psychogenic factors, nutrition, preoperative care, anesthesia, postoperative care, pain, complications, shock, and many other essential topics. This book fills a gap in surgical literature.

1) Amenorrhea. By Lawrence M. Randall, M.D. and Thomas W. McElin, M.D. Charles C. Thomas, Publisher. Springfield, Ill., 1951. 74 pages. Cloth. $2.25.

2) Wounds of the Extremities in Military Surgery. By Oscar P. Hampton. St. Louis. The C. V. Mosby Company, 1951. 434 pages. Cloth. $10.

3) Cunningham's Textbook of Anatomy. Edited by James Cooper Brash, M.D. Oxford University Press, London-New York, 1951. 9th ed., 1604 pages. Cloth. $14.

4) Surgical Care. A Practical Physiologic Guide. By Robert Elman, M.D. Appleton-Century, Crofts, Inc. New York, 1951. 586 pages. Cloth.

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